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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/077,572	10/13/98	APICELLA M	875001US2

HM12/1011
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EXAMINER	
DEVI,S	
ART UNIT	**PAPER NUMBER**
1645	25

DATE MAILED: 10/11/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/077,572	Apicella et al.
Examiner	**Group Art Unit**
S. Devi, Ph.D.	1645

☒ Responsive to communication(s) filed on *Aug 16, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *22-26, 29, 32, and 33* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *30 and 31* is/are [redacted] *cancelled*.

☒ Claim(s) *22-26, 29, 32, and 33* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Change of Art Unit Location

1) Effective 20 June 2000, the Art Unit location of the instant application in the US PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1645.

Request for Continued Prosecution Application

2) The request filed 08/16/2000 (paper no. 24) for a Continued Prosecution Application (CPA) under 37 C.F.R 1.53(d) based on the parent Application, SN 09/077,572, is acceptable and a CPA has been established. An action on the CPA follows.

Applicants' Amendment

3) Acknowledgment is made of Applicants' amendment filed 07/12/00 (paper no. 19) in response to the Final Office Action mailed 01/04/00 (paper no. 16).

Status of Claims

4) Claims 30 and 31 have been canceled via the amendment filed 06/12/00.

Claims 22, 23 and 29 have been amended via the amendment filed 06/12/00.

New claims 44 and 45 have been added via the amendment filed 06/12/00. These claims have been misnumbered. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 44 and 45 have been renumbered as claims 32 and 33 respectively.

Claims 22-26, 29, 32 and 33 are pending and are under examination.

Declaration under 37 C.F.R § 1.132

5) Acknowledgment is made of Applicants' (Drs. Gibson and Apicella) declaration filed 07/12/00 (paper no. 9) under 37 C.F.R § 1.132.

Prior Citation of Title 35 Sections

6) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

7) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Maintained

8) The objection to the drawings made in paragraph 6 of the Office Action mailed 04/28/99 (paper no. 11) under 37 CFR 1.84 because of the reasons set forth by the Draftsperson is maintained for reasons set forth therein. Applicants assure the Office that corrected formal drawings will be submitted upon notification of allowance of the claims.

Rejection(s) Moot

9) The rejection of claims 30 and 31 made in paragraph 16 of the Office Action mailed 01/04/00 (paper no. 16) under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

10) The rejection of claims 30 and 31 made in paragraph 17(e, f and g) of the Office Action mailed 01/04/00 (paper no. 16) under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the new matter issue, is moot in light of Applicants' cancellation of the claims.

11) The rejection of claim 31 made in paragraph 20 of the Office Action mailed 01/04/00 (paper no. 16) under 35 U.S.C § 103(a) as being anticipated by Karow *et al.* (*J. Bacteriol.* 174: 7407-7418, 1992) in view of Gupta *et al.* (*Infect. Immun.* 60: 3201-3208, 1992), is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

12) The rejection of claim 29 made in paragraph 16 of the Office Action mailed 01/04/00 (paper no. 16) under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the new matter issue, is withdrawn in light of Applicants' amendment to the claim.

13) The rejection of claim 22 made in paragraph 17(a) of the Office Action mailed 01/04/00 (paper no. 16) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

14) The rejection of claim 23 made in paragraph 17(c) of the Office Action mailed 01/04/00 (paper no. 16) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

15) The rejection of claim 29 made in paragraph 17(d) of the Office Action mailed 01/04/00 (paper no. 16) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

16) The rejection of claim 22 made in paragraph 17(e) of the Office Action mailed 01/04/00 (paper no. 16) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

17) The rejection of claim 22 made in paragraph 19 of the Office Action mailed 01/04/00 (paper no. 16) under 35 U.S.C § 102(b) as being anticipated by Karow *et al.* (*J. Bacteriol.* 174: 7407-7418, 1992) is withdrawn in light of Applicants' amendment to the claim.

18) The rejection of claims 23-26 made in paragraph 20 of the Office Action mailed 01/04/00 (paper no. 16) under 35 U.S.C § 103(a) as being anticipated by Karow *et al.* (*J. Bacteriol.* 174: 7407-7418, 1992) in view of Gupta *et al.* (*Infect. Immun.* 60: 3201-3208, 1992) is withdrawn in light of Applicants' amendment to the claims or the base claim.

Rejection(s) Maintained

19) The rejection of claims 22, 23, 25 and 29 made in paragraph 9 of the Office Action mailed 04/28/99 (paper no. 11) under the judicially created provisional obviousness type double patenting is maintained for reasons set forth therein. Applicants state that if appropriate, they will consider filing a terminal disclaimer upon notification of allowable subject matter.

20) The rejection of claims 22-26 and 29 made in paragraph 10 of the Office Action mailed 04/28/99 (paper no. 11) under 35 U.S.C. § 112, first paragraph, with regard to the deposit of the mutant bacterium is maintained for reasons set forth therein. Applicants assure the Office that

upon receiving indication of allowable subject matter, Applicants will deposit plasmids pB28 and pB29 in compliance with 37 CFR 1.801-1.809.

The Applicants' Declaration under 37 C.F.R § 1.132

21) Applicants state that the Karow *htrB* mutant has a set of lipid A structures different in from the *htrB* mutant pathogens of the present invention as analyzed by a mass spectrometric examination. Applicants assert that the *htrB* mutation in *N. gonorrhoeae* strain 1291 results in the complete deletion of one of the two lauric acid moieties to form a pentaacyl lipid A structure and that the *htrB* knockout in *H. influenzae* produces a truncated pentaacyl and tetraacyl lipid A species. Applicants, however, acknowledge that Karow's *E. coli* mutant contains pentaacyl and tetraacyl substituted lipid A species, but contend that these structures contain at least one new fatty acid.

The information in the Applicants' Declaration has been carefully considered. However, as drafted currently, instant claims are obvious over the teachings of Karow *et al.* (*J. Bacteriol.* 174: 7407-7418, 1992) in view of Westphal *et al.* and/or Gupta *et al.* as described below under art rejections. Instant claims, as drafted currently, do not contain, as limitations, the mass spectrometric differences found in the mutants of the instant invention compared to that of the prior art mutant or mutant endotoxin, i.e., Karow's mutant or mutant endotoxin. Instant claims do not include, as limitations, the presence only of truncated pentaacyl and tetraacyl lipid A species, the absence of fully acylated lipid A, and/or the absence of at least one new fatty acid in the instantly claimed mutants. Therefore, Karow *et al.* is a valid art and is properly applied to reject instant claims.

New Rejections

Applicants are asked to note the new rejections made in this Office Action. The Applicants' amendment including the addition of new claims, necessitated the new ground(s) of rejection presented in this Office Action.

Double Patenting

22) The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23) Claim 32 is provisionally are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 25 and 27 of the copending Application, SN 09/565,943. Although the conflicting claims are not identical, they are not patentably distinct from each other. The invention claimed in the instant claim is encompassed in the scope of the above-mentioned claims of the co-pending application. M

This is a provisional obviousness-type double patenting rejection, because the conflicting claims have not in fact been patented.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

24) Claims 22, 29, 32 and 33 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure, because the specification does not provide evidence that the biological materials of the claimed invention are (1) known and readily available to the public; (2) reproducible from the written description, e.g. sequenced; or (3) deposited.

It appears that the claimed *htrB* mutant Gram-negative bacterial pathogens as recited in instant claims are required to practice the claimed method of making and using the product, mutant endotoxin, of the instant invention. As required elements, the mutant bacteria must be known and readily available to the public, or obtainable by a reproducible method set forth in the specification. It is unclear if the mutant bacteria are publicly available, or can be reproducibly

isolated from nature without undue experimentation. Therefore, suitable deposits for patent purposes are suggested. The specification appears to lack complete deposit information for any of the *htrB* Gram-negative mutant bacterial pathogens that are specifically recited in instant claims. Without a publicly available deposit of the recited bacterial mutants, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed.

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent on this application and that the deposit will be replaced if viable sample cannot be dispensed by the depository, is required to satisfy the deposit requirements. See 37 CFR 1.801-37 CFR 1.809. Further, the statement should identify the deposited mutant bacterial pathogens by their depository accession number, establish that the deposited mutant bacterial pathogens are the same as that described in the specification, and establish that the deposited bacterial pathogens were in Applicants' possession at the time of filing. *In re Lundak*, 773 F2d 1216, 227 USPQ 90 (Fed. Cir. 1985).

Rejection under 35 U.S.C. § 103(a)

25) Claims 22, 23, 25 and 32 are rejected under 35 U.S.C § 103(a) as being unpatentable over Karow *et al.* (*J. Bacteriol.* 174: 7407-7418, 1992, already of record) in view of Westphal *et al.* (*Methods Carbohydr. Chem.* 5: 83-91, 1965, already of record).

Karow *et al.* teach a method of making an endotoxin or LPS from a Gram negative bacterial pathogen, *E. coli*, containing a mutated *htrB* gene. The mutant bacterium produces a mutant endotoxin lacking one or more lauric acid and myristic acid (i.e., secondary acyl chains of lipid A) (see abstract; page 7413 left column; paragraph bridging left and right columns on page 7416, and page 7409, left column, under 'Fatty acid analysis'). The description provided in the Figure 4 legend indicates that the *htrB* mutant endotoxin is isolated from the *htrB* mutant bacterium (see page 7413). The lauric acid and myristic acid contents of the LPS form *htrB*

bacterial pathogen was reduced compared to that of wild type bacterial pathogen (see Figure 4 and page 7413). A method of making a *htrB* mutant of *E. coli* is also taught (see abstract and 'Materials and Methods'). That the absence of one or more lauric acid and myristic acid in the lipid A renders the bacterial LPS substantially less toxic compared to the wild type *E. coli* is inherent from the teachings of Karow *et al.*

Karow *et al.* do not expressly disclose a method of purifying the mutant endotoxin by phenol-water extraction, or a method of making of a *htrB* mutant of *Haemophilus, Neisseria, Moraxella, Campylobacter, Shigella or Pseudomonas,* or a *htrB* mutant endotoxin from these pathogens.

However, the method of purifying an endotoxin, for example, by phenol-water extraction is conventional and is well known in the art for decades. For instance, Westphal *et al.* teach phenol-water extraction of Gram negative bacterial lipopolysaccharides (see pages 86-90).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to purify Karow's *E. coli htrB* mutant endotoxin lacking one or more myristic acid substitutions in the lipid A using Westphal's phenol-water extraction method to produce the endotoxin of the instant invention, since Westphal's phenol-water extraction method is the widely used conventional method of purifying endotoxin. One skilled in the art would have had a reasonable expectation of success in obtaining a *htrB* mutant bacterium or a *htrB* mutant endotoxin from other Gram negative bacterial pathogens, such as, *Haemophilus*, *Neisseria*, *Moraxella*, *Campylobacter*, *Shigella* or *Pseudomonas* by extending Karow's method of making an *htrB* mutant *E. coli* bacterium or an *htrB E. coli* mutant endotoxin to one of these pathogens, since the lipid A parts of the LPS of *E. coli* and the Gram negative bacteria recited in claims 32 and 33 are structurally and/or biologically conserved with a similar genetic or biosynthetic make-up. Extending the Karow's method used for one Gram negative bacterial pathogen or its endotoxin, to another Gram negative pathogen or its endotoxin having a conserved lipid A would have been obvious to a skilled artisan and would have expected to bring about similar effects, absent evidence to the contrary.

Claims 22, 23, 25 and 32, as a whole, are obvious over the prior art of record.

26) Claims 24, 26, 29 and 33 are rejected under 35 U.S.C § 103(a) as being unpatentable over Karow *et al.* (*J. Bacteriol.* 174: 7407-7418, 1992, already of record) in view of Westphal *et al.* (*Methods Carbohydr. Chem.* 5: 83-91, 1965, already of record) as applied to claims 22, 23 and 25 above, and further in view of Gupta *et al.* (*Infect. Immun.* 60: 3201-3208, 1992, already of record).

The teaching of Karow *et al.* as modified by Westphal *et al.* is explained above, which does not disclose conjugating the mutant endotoxin to a carrier protein, or raising antisera to the mutant endotoxin in an individual.

However, methods of conjugating a substantially less toxic endotoxin of a Gram negative bacterial pathogen to a carrier protein to enhance the immunogenicity of the endotoxin are well known and widely practiced in the art. For instance, Gupta *et al.* teach a method of conjugating a deacylated endotoxin of a Gram negative bacterial pathogen to a carrier protein to produce an immunogenic conjugate vaccine that can be used to raise endotoxin-specific antisera by administering it to an individual animal (see abstract, and pages 3202 and 3203).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate Karow's endotoxin as modified or purified by Westphal *et al.* to a carrier protein and raise endotoxin-specific antisera as taught by Gupta *et al.* One skilled in the art would have had a reasonable expectation of success in conjugating Karow's endotoxin as modified or purified by Westphal *et al.* to a carrier protein to produce a conjugate for use as a vaccine formulation, or as an immunogen to raise endotoxin-specific antisera of the instant invention, since the *htrB* mutant endotoxin lacking secondary acyl chains is expected to function significantly no differently in a conjugate than the deacylated endotoxin taught by Gupta *et al.* Extending such a method used for one Gram negative bacterial endotoxin, to another Gram negative pathogen endotoxin having a conserved lipid A, such as, those recited in claim 33 would have been obvious to a skilled artisan and would have expected to bring about similar effects, absent evidence to the contrary.

Claims 24, 26, 29 and 33, as whole, are *prima facie* obvious over the prior art of record.

Objection(s)

27) Claims 32 and 33 are objected to for the following reasons:

(a) Claims 32 and 33 are objected to for not italicizing the names of the bacterial genera: "Haemophilus, Neisseria, Moraxella, Campylobacter, Shigella or Pseudomonas". To be consistent with the practice in the art, it is suggested that Applicants replace the recitation with -- *Haemophilus*, *Neisseria*, *Moraxella*, *Campylobacter*, *Shigella* or *Pseudomonas*--.

Remarks

28) Claims 22-26, 29, 32 and 33 stand rejected.

29) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1 (CM1). The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242.

30) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. The Examiner can normally be reached on Monday to Friday from 8.00 a.m to 4.00 p.m.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SD
S. Devi
Patent Examiner
September 2000